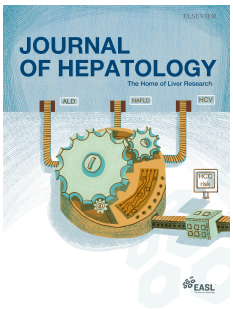
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



Immune-mediated hepatitis with the Moderna vaccine, no longer a coincidence but confirmed.

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Immune-mediated hepatitis with the Moderna vaccine, no longer a coincidence but confirmed.

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To the editor:

We have read with interest the recent cases suggesting the possibility of vaccine-induced immune-mediated hepatitis with Pfizer-BioNTech and Moderna mRNA-1273 mRNA vaccines for the SARS-CoV-2 virus. (1-7). However, as the cohort of vaccinated individuals against COVID-19 increases, the previously reported cases could not exclude a coincidental development of autoimmune hepatitis, which has an incidence of 3/100 000 population per year (8). Our case demonstrates conclusive evidence of vaccine-induced immune-mediated hepatitis with a rapid onset of liver injury after the first Moderna dose, which on re-exposure led to acute severe autoimmune hepatitis.

Case description

47-year-old Caucasian man, previously completely well, received 1st Moderna vaccine dose on the 26 April 2021. He noted malaise and jaundice three days after. Investigations on the 30th April showed serum bilirubin 190 µmol/L (normal 0-20), ALT 1048 U/L (normal 10-49), ALP 229 U/L (normal 30-130), albumin 41 g/L (normal 35-50). Blood count, renal function and INR were normal. Liver function tests (LFTs) last checked 4 years previously were normal. He denied paracetamol use and reported minimal alcohol intake. Ultrasound scan, CT thorax, abdomen and pelvis and MRI pancreas performed to exclude malignancy, showed no significant findings. Serum IgG was raised at 25.1 g/L (normal 6-16), IgM 2.2 g/L(0.5-2) and serum was positive for Anti-Nuclear Antibody. Serological tests for HAV, HBV, HCV, HEV, EBV and CMV were negative.

His jaundice faded and LFTs improved: bilirubin falling on 25th June to 69 µmol/L and ALT to 332 U/L. The patient received his 2nd Moderna vaccine dose on the 6 July 2021 (despite reporting the jaundice to the vaccination centre) and the jaundice returned a few days after. Blood tests on 20th July found bilirubin 355 µmol/L, ALT 1084 U/L and a raised PT 18.4 seconds. After liver biopsy on the 21st July 2021 he was commenced onto Prednisolone 40 mg/day and was transferred to our service.

On examination, he was alert, deeply jaundiced, with hepatomegaly but no ascites. Repeat abdominal ultrasound showed a mildly fatty liver, patent portal and hepatic vein flow, with no ascites. Review of the liver biopsy showed acute active hepatitis: widespread areas of

bridging necrosis, marked interface hepatitis, lymphoplasmatic inflammation including eosinophils, ballooned hepatocytes, multi-nucleated giant cells, and emperipolesis (Figure 1). There was minimal fibrosis, Ishak stage 1. The pattern of injury on histology was consistent with acute hepatitis, with features of autoimmune hepatitis or possible drug-induced liver injury (DILI), triggering an autoimmune-like hepatitis.

Prednisolone 40 mg/ day was continued and LFTs improved (Figure 1). He was discharged on Prednisolone and on follow-up, blood tests continue to improve, and PT normalised within 2 weeks.

Discussion

This case illustrates immune-mediated hepatitis secondary to the Moderna vaccine, which on inadvertent re-exposure led to worsening liver injury with deranged synthetic function. This occurred in a well man with no other medical problems. The onset of jaundice associated with the mRNA vaccine was unusually rapid. This was also illustrated in the other cases where symptoms developed over a median of 7 days (range 4-35). Latency is usually longer in other causes of drug induced liver injury, but can vary depending on mode of injury.
The mRNA vaccine pathway triggers pro-inflammatory cytokines including interferon and cross-reactivity has been illustrated between the antibodies against the spike protein and self-antigens (9-10).

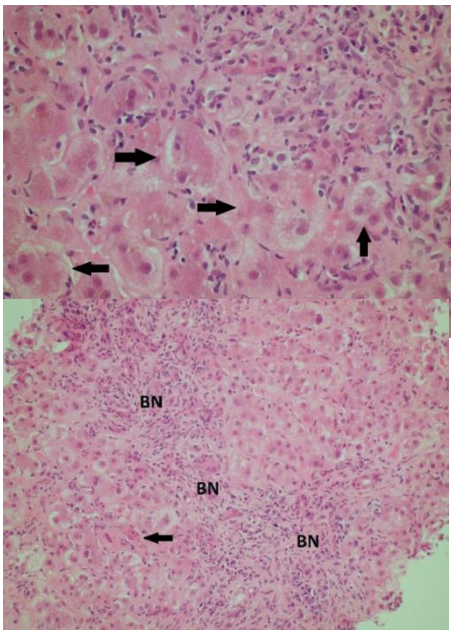
7 cases of suspected immune-mediated hepatitis have been reported with SARS-2-COV mRNA vaccines (three with Pfizer and four with Moderna) (1-7). Liver histology was assessed in every case and findings were similar to ours indicating acute hepatitis with interface hepatitis, lymphoplasmacytic infiltrate and absence of fibrosis. Eosinophils as part of the infiltrate, which can be noted in DILI were present in three cases. All seven patients responded well to steroids (n=5 Prednisolone, n=1 Budesonide and n=1 Methylprednisolone). In three cases there were features suggesting coincidental autoimmune hepatitis: 35-year-old lady in her third trimester of pregnancy with positive double stranded DNA, an 80-year-old lady with a history of autoimmune conditions and a 41-year-old lady with strongly positive auto-antibody panel after both doses of vaccination. In the other four cases, a raised IgG, with at least one positive antibody was noted in three cases (4-7).

This case has confirmed immune-mediated hepatitis secondary to the Moderna vaccine,

which on inadvertent re-exposure led to acute severe hepatitis. Treatment with corticosteroid therapy appears to be favourable. We wish to highlight that immune-mediated reactions from the SARS-CoV-2 mRNA vaccines are very rare and during the COVID pandemic, the vaccination programme continues to be crucial. We report this case to encourage vigilance for drug-induced reactions and to raise awareness to vaccination centres to incorporate it into their routine checks before administering second doses. Long-term follow up of identified individuals will be essential in determining the prognosis of this immune-mediated liver injury.

a)

b)



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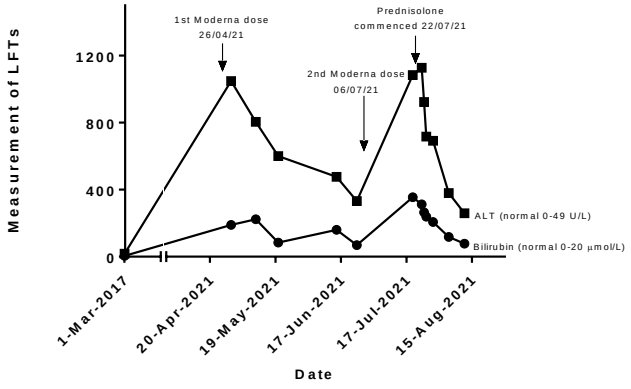

Figure 1. Histological findings and biochemical findings.

Haematoxylin & Eosin (H&E)-stained section of liver biopsy indicates acute hepatitis. (a) The parenchymal hepatocytes are arranged into rosette forms (marked with arrows) with cholestasis. (b) Bridging necrosis (BN) from hepatocyte loss, some by apoptosis (arrow). (c) Diagram showing trend of Bilirubin and ALT following Moderna vaccine dose one and two with response to prednisolone.

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